Interpretative Differences Between Massachusetts' and California's Perchlorate Health Assessments

Prepared By

Office Of Research And Standards
Massachusetts Department Of Environmental Protection
1 Winter Street
Boston, MA 02043 USA

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INTRODUCTION

The Massachusetts Department of Environmental Protection (MA DEP) completed in January 2004 a technical assessment of the toxicity and health effects of perchlorate that was released in May 2004 (MA DEP, 2004). In that document, MA DEP identified a chronic oral reference dose (RfD) of 3×10^{-5} mg/kg-d. This RfD would be associated with a drinking water exposure limit of 1 ug/L using standard exposure assumptions and methodologies used to derive drinking water guidance. The State of California recently released its most current assessment of the toxicology and health effects of perchlorate (CA OEHHA, 2004) in which it identified a Public Health Goal for perchlorate in drinking water of 6 ug/L. Given that the same data sets were available to both agencies for their respective evaluations and guidance development and that the agencies have reached differing conclusions about the appropriately protective concentration of perchlorate in drinking water, MA DEP has prepared the following set of questions and answers related to the two groups conclusions and its position on the issue.

- **Why Did MA DEP Use a Weight of the Evidence Approach Rather Than Rely Solely On The Greer (2002) Study Performed on Human Volunteers?**

The Greer study, although very informative, has a number of inherent limitations that introduce considerable uncertainty when the study's results are extrapolated to long-term exposures of infants and other susceptible people to perchlorate. These limitations include:

1) The study included only a small number of people, from 7-10, per dose group.
2) Only healthy adults were included—known sensitive subgroups such as pregnant women, infants, children, those suffering from thyroid insufficiency and those with iodide insufficiency were not included in the study (indeed many of these groups could not be included due to ethical concerns)
3) The study was of short duration, precluding evaluation of potential longer-term effects.

Despite these limitations, the Greer study is very useful in that it provides quality data on the degree to which perchlorate interferes with iodine uptake by the human thyroid. Thus, MA DEP did include this study in its assessment. However, because of the limited nature of this study, MA DEP chose to use a weight of the evidence approach, which considered additional data on effects of perchlorate on fetal and neonatal development, in assessing perchlorate toxicity.

In addition, MA DEP concluded that the Greer study results themselves support a lower interim exposure guidance value for sensitive individuals than that adopted by CA EPA.

- **Why Did MA DEP Derive a Lower Interim Exposure Guidance Value for Perchlorate than CA EPA?**

Data from the Greer study was used by CA EPA to calculate a perchlorate dose associated with a 5% decrease in iodide uptake in the thyroid using a benchmark dose approach. The 95% lower confidence limit on this dose was 0.0037 mg/kg-day. CA EPA used this benchmark dose $_{\text{lower 95\% CI}}$ (BMDL) as the starting point, or point of departure (POD), in deriving their public health goal of 6 ppb perchlorate in drinking water. The POD is the dose estimate from which an acceptable human exposure value is derived using adjustments to account for uncertainties in the available scientific information as well as differences in exposures.

For the reasons discussed below, MA DEP has concluded that the currently available data support a lower value in order to be sufficiently protective of sensitive individuals, including pregnant women and infants.

1) **Uncertainty Regarding Selection of the Starting Point or POD**. The CA EPA BMDL estimate from the Greer study is higher than that derived recently by US EPA scientists (who helped develop and have extensive experience with the methods used to calculate BMDL values). Based on their evaluation of the Greer study, US EPA derived a BMDL value of 0.002 mg/kg-day, which is about 2-fold lower than the estimate derived by CA EPA (0.0037 mg/kg-day). The recent US EPA estimate was not considered in the CA EPA perchlorate assessment report, probably due to timing issues. MA DEP has reviewed both the CA EPA and US EPA BMDL analyses. Although the CA EPA calculations were of high quality and were appropriately conducted, the recent US EPA analyses were more robust in scope. US EPA considered multiple data sets from the Greer study and data outliers were addressed. Accounting for this difference alone, would result in a PHG of 3 ppb.

   In part because of uncertainty over what level of iodide uptake inhibition constitutes an adverse effect (as discussed in more detail below, modeling data suggests that 5% inhibition of iodide uptake may be associated with adverse effects), MA DEP used a traditional no observed adverse effect level (NOAEL) approach rather than a benchmark approach to establish a POD. This approach is computationally simpler, more transparent and, given the uncertainty in selection of the target response level, no less accurate. Using this approach, MA DEP determined that the results of the Greer study support an exposure of 0.007 mg/kg-day as a minimum effect level. This value was selected as the POD. MA DEP applied an uncertainty factor (UF) of 3 to this minimum effect level value to derive a NOAEL estimate of approximately 0.002 mg/kg-day. This value is the same as the POD derived by US EPA in their recent BMDL analysis. Thus, the US EPA BMDL analysis and the MA DEP approach using the simpler NOAEL methodology yield values about 2-fold lower than that derived by CA EPA.

2) Choice of Uncertainty Factors to Account for Scientific Uncertainty and to Protect the Health of All Citizens

Because of concern for children's health, MA DEP also choose a more health protective approach when accounting for uncertainties in the scientific information on perchlorate's toxicity. CA EPA used a total uncertainty factor of 10 to account for all uncertainty in deriving their PHG. As discussed below, based on its review of the data, MA DEP scientists concluded that a higher UF was needed. These uncertainties are discussed below.

Interindividual Variability in Sensitivity. CA EPA used a single UF of 10 (or in the case of infants, only 3), to account for *all* uncertainty in the derivation of its PHG. An uncertainty factor of 10 is used in most federal and state environmental programs to account for inter-individual variability in sensitivity to chemicals attributable to differences in how individuals absorb, process and excrete toxins (pharmacokinetics) and differences in physiological responses. Evaluations of variations in sensitivity to toxic chemicals indicate that a factor of 10 accounts for inter-individual variability in most cases. However, for some chemicals, experimental data indicate that such differences are smaller than 10-fold and in others substantially larger. An UF for inter-individual variability is needed in this case because the underlying study involved a small number of healthy adults likely to be iodide sufficient, and did not include sensitive members of the population.

MA DEP concluded that an UF of 10 was needed to account for differences in sensitivity to perchlorate even among infants. In its assessment, CA EPA applied an UF of 3 when considering risks to infants, arguing that a full factor of 10 was not needed because a dose adjustment was applied to account for size and drinking water consumption differences between adults and infants. They also cite earlier US EPA documents as indicating that only minor differences in perchlorate pharmacokinetics exist between adults and infants, supporting a smaller UF. However, US EPA guidelines state that reduction of the intraspecies UF from 10 should be considered only if data are sufficiently representative of the exposure/response data for the most susceptible populations. MA DEP concluded that this was not the case for perchlorate. Additionally, US EPA notes in their October 2003, responses to comments received on their perchlorate review, that the fetus and infant in fact have different dosimetry than adults because they are dependent on iodide delivery from the placenta and mammary tissues. Thus, EPA also concluded that an UF of 10 is warranted when extrapolating from the Greer study to infants and fetuses. MA DEP's Scientific Advisory Committee also recommended that a full UF of 10 be used to account for variability in sensitivity among infants. MA DEP scientists have concluded that, even adjusting for exposure differences, perchlorate's mechanism of action suggests that infants, because of limited stores of thyroid hormones and differing dosimetry, potentially limited iodide intake and ongoing neurological development, may well be greater than 3-fold more sensitive to perchlorate compared to the adults included in the

Greer study. Additionally, variation *among* infants in sensitivity, for example due to differences in dietary iodine intake, genetic factors etc, is also likely.

If one applies a 10-fold UF for infants rather than 3-fold, this adjustment alone would reduce the PHG (for infants) to 2 ppb. Combined with the lower POD (as discussed above) the PHG would be 1 ppb.

Other Uncertainties. In its initial draft document CA EPA included an additional UF of 3 to account for database deficiencies when extrapolating from the Greer study to the whole population. This UF was not included in their final report. Because of the many residual uncertainties, as briefly summarized below, MA DEP has concluded that a larger composite uncertainty factor is warranted when extrapolating from the Greer study to the whole population.

Some of these additional uncertainties include:

a. **Duration of Exposure Uncertainty**. The Greer study was only 14 days in duration. Effects might well have been detected at lower doses in this study with longer-term exposures.
    i. Some have argued that longer exposures would not influence toxicity because perchlorate does not accumulate in the body. However, perchlorate accumulation in the thyroid at low doses has not been ruled out and the downstream effects of perchlorate may themselves be cumulative (e.g. depletion of stored thyroid hormones). In fact, a recent US EPA analysis of the Greer study itself indicates that perchlorate effects were greater at later time points in that study, supporting a duration of exposure effect over a relatively short period of 2-weeks. In risk assessment, when extrapolating from shorter-duration studies to long-duration exposures, as could occur from the consumption of drinking water, an UF of from 3-10 is usually included, unless compelling data exists to demonstrate that this is not appropriate.

b. **Uncertainty as to the Appropriate Level for the Starting Point or POD.** CA EPA treated the benchmark dose associated with a 5% inhibition of iodide uptake in healthy adults as a no adverse effect level (i.e. that such inhibition would not result in any adverse physiological effects). However, significant effects, including changes in thyroid hormone status and brain development, have been reported in animals exposed to perchlorate at doses associated with predicted iodide uptake inhibition of ***as low as 1.5%*****,** based on a physiologically based pharmacokinetic model developed in large part by military scientists. Although there has been debate about the quality of the data on the brain development effects and over the physiological significance of the reported thyroid hormone changes, the mechanistic concordance between these observations combined with fundamental uncertainty over the level

and timing of hormone concentration changes with respect to fetal and neonatal neurological development, argue for caution in selecting a NOAEL. The 5% inhibition level could reasonably be treated as an effect level, suggesting use of an additional UF or the use of a 1% iodide uptake inhibition level (rather than a 5% level) as the POD. Either option would result in a lower PHG.

c. **Uncertainties regarding mode of action**.
   i. The kinetics, dose response and impacts of perchlorate induced discharge of stored iodide from the thyroid, which has been reported to occur, and which would be expected to exacerbate the effects of concurrent blockage of iodide uptake, has not been fully addressed. If iodide discharge occurs at low doses concomitant with blockage of uptake, depletion of thyroidal iodide and hormone stores could occur over longer exposure durations.
   ii. The potential physiological significance of perchlorate inhibition of the thyroid pendren protein has not been elucidated.
   iii. Uncertainties remain about the mode of action and kinetics of inhibition of iodide uptake. Whether perchlorate is transported intracellularly, as previously assumed, is now questioned. The duration of the "blockage" of function at the level of the receptor is also uncertain and potential non-reversible effects, for example due to receptor-ligand "aging", have not been fully addressed.
   iv. The development of tumors in offspring of animals maternally exposed to perchlorate raises concern regarding long-term changes in physiological status, or "imprinting", as a result of *in utero* exposures.
   v. Emerging data on the importance of cyclical variations in thyroid hormone levels in development (which would require close tracking of thyroid hormone status in response to perchlorate, which has not routinely been done), as well as questions about the sensitivity of the thyroid hormone assays used to detect small but potentially significant changes, would both bias the thyroid hormone results of various studies towards the null hypothesis of no perchlorate effect. More extensive diurnal sampling and use of more sensitive assays could well result in a lower effect level.
   vi. Potential interactions of perchlorate with other thyroid toxicants, especially ones that interact with other targets, are also of concern and have been not addressed.

MA DEP scientists have concluded that, taken together, these uncertainties necessitate a composite uncertainty factor well in excess of 10-fold, when extrapolating from the results of the Greer study to sensitive subgroups in the population. If using the benchmark dose approach and data from the Greer study, use of a composite UF of at least 30 is clearly justified and values of from100-300 can be supported. Combined with the lower POD derived by US EPA for the Greer study, drinking water guidance values

to protect sensitive subgroups of from approximately 1 ppb to the sub ppb range would result.

In choosing a drinking water interim guidance value for sensitive groups of 1 ppb, MA DEP used a weight of the evidence approach that considered additional data, including results from more extensive studies on biological responses to perchlorate in animals. These studies assessed a number of additional endpoints beyond iodide uptake inhibition and evaluated the effects of perchlorate on the developing fetus and nursing neonate. By relying on studies of healthy adults *and* younger life stages, as well as more thoroughly accounting for uncertainties in the science, MA DEP is recommending a lower limit than California for sensitive subgroups. Although a value below 1 ppb can be supported on the basis of the toxicity data, sampling and laboratory methodologies in use are not capable of routine, accurate measurements of perchlorate in drinking water below 1 ppb. Thus, 1 ppb was selected as the interim guidance level.

REFERENCES

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